REMARKS

Claims 1-29 are pending. The Applicant herein respectfully requests further examination of the application and reconsideration of the claims, in view of the amendments and remarks presented herein.

Objections to the Specification and Claims

The Applicants herein present amendments to the Specification and Claims specifically as recommended by the Examiner. Accordingly, since all objections set forth by the Examiner are now fully addressed as recommended by the Examiner, the Applicants respectfully request the Examiner to withdraw all objections to the specification and claims.

Rejection under 35 USC §112, pargraph 1

The Applicants first thank the Examiner for acknowledging that the subject matter of the claims with regard to 'method of treatment', i.e., a method for the treatment of a cholesterol-associated tumor, is enabled in view of the specification. The Examiner, however, has rejected the subject matter of the pending claims with regard to "prevention" under 35 USC §112, paragraph 1 as not being enabled in view of the specification.

The Applicants respectfully point out the purpose of the requirement that the specification describe the invention in such terms that one skilled in the art can make and use the claimed invention, i.e., enablement, is to ensure that the invention is communicated to the interested public in a meaningful way. MPEP §2164. The Applicants have particularly discovered that pathological mechanisms of cholesterol-associated tumors are intimately related to the intestinal absorption of cholesterol and, accordingly, both the ability to control the conditions *in vivo* that mediate as well as advance tumor development are of paramount pharmacological value. All that is required is that the specification teach one of ordinary skill in the art how to make and use the invention (to prevent and to treat cholesterol-associated tumors). If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 USC§112 ¶1 is satisfied. MPEP §2164.01(c). What is disclosed and claimed is in fact is a new use of a known compound,

ezetimibe, for example. As further pointed out *infra*, the preventative efficacy of azetidinone-based cholesterol absorption inhibitors with regard to cholesterol-associated tumors has not previously been recognized. However, since oral administration of azetidinone compounds inhibit both dietary and biliary cholesterol absorption and resorption in the intestinal tract, the prevention of cholesterol-associated tumors mediated by such absorption and resorption is readily attainable by one of ordinary skill in the art particularly according to the disclosure set forth at pages 9-11 of the instant Specification.[1]

Nevertheless, while reserving the right to file a separate application drawn toward the disclosed methods of prevention, in order to expedite the prosecution of this case, the Applicants herein remove the term "prevention" from all method of use claims now pending. Accordingly, the Applicants respectfully request the Examiner to withdraw the rejection.

Rejection under 35 USC §112, pargraph 2

In order to expedite the prosecution of this case, the Applicants herein remove the term "essentially" from all claims now pending which refer to Markush groups of specified compounds. Accordingly, the Applicants respectfully request the Examiner to withdraw the rejection.

Rejection under 35 USC §103(a)

The Examiner has rejected the subject matter of claims 1-14, 16-21, and 23-29 as obvious to one of ordinary skill in the art at the time of the invention. Particularly, it is alleged that one of ordinary skill in the art would have been motivated to use azetidinone compounds taught by Schering Corporation (Dugar, Rosenblum, and Burnett), to treat benign and malignant prostate tumors since azetidinone compounds were known in the art at the time of the invention to control cholesterol absorption. The issue, however, boils down to whether the Applicants' described and claimed invention - i.e., the new pharmacological application for azetidinones - was 1) suggested; and, 2) the results were not unexpected to one of ordinary skill in the art at the time of

[1] The patent specification must disclose information sufficient to enable those skilled in the art to make and use the claimed invention; however, the fact that some experimentation is required to practice the claimed invention is permissible, so long as it is not undue. Atlas Powder Co. v. E.I. DuPont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).

the invention in view of several obscure 20-year old references (cited by the Applicants) to uses of anionic exchange resins, polyene macrolides, and phytosterols to control lipid metabolism and effect tumorigenesis. The Applicants also highlight the longfelt need addressed by the Applicants' invention as a considerable factor in the analysis of the facts under 35 USC §103.[2]

The Applicants first respectfully point out that the references relied upon by the Examiner to illustrate the correlation between the metabolism of lipids and cholesterol and tumor etiology are each over twenty (20) years old.[3] Moreover, the Applicants respectfully highlight to the Examiner that the azetidinones are not even remotely structurally related to the anionic exchange resins, polyene macrolides, or phytosterols used in the prior art to control lipid metabolism. The Applicants, furthermore, briefly highlight the current art-accepted relationship of tumor etiology to cholesterol metabolism.[4] The Applicants particularly illustrate herein that more recently there is a significant teaching away from the concept of cholesterol, *per se*, being identified or targeted as a causative agent of tumor promotion. In sharp contrast, current art-accepted models implicate metabolites upstream to the biosynthesis of cholesterol, i.e., upstream precursor isoprenoids, geranylgeranyl and farnsylpyrophosphate as causative agents in tumorigenesis. This current art-accepted model is manifested by more recent results interpreted from clinical studies of statins. Particularly, HMG-CoA reductase inhibitors function at an early step in the synthesis of cholesterol; as a consequence, the levels of cholesterol, and its upstream precursor isoprenoids, geranylgeranyl and farnsylpyrophosphate, are reduced. Thus, essential cell components that require isoprenoids, e.g. dolichols and ubiquinone (a polyisoprenylated quinoid cofactor of the

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[2] "Longfelt need" for a solution to a problem was originally articulated as a factor in the obviousness analysis in the seminal Supreme Court decision Graham v. Deere Graham v. John Deere Co., 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966).

[3] All were cited by the Applicants in the Specification, e.g., Schaffner (primary inventor), in 1983 published,: "Benign Prostatic Hypertrophy", Frank Hinman, Jr. ed. Springer-Velag, New York, pp.280-307 wherein clinical studies with candicidin and other polyene macrolides were reviewed. Candicidin in long-term rat studies has been shown to inhibit tumor initiation and progression as compared to untreated controls. The Applicants respectfully point out, however, it is improper, in determining whether a person of ordinary skill would have been led to this combination of references, simply to "[use] that which the inventor taught against its teacher." W.L. Gore v. Garlock, Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

[4] *See*, Appendix I attached hereto.

electron transport chain), are affected by HMG-CoA reductase inhibitors. Anti-cancer effects of statins, for example, is currently ascribed in the art to the loss of the isoprenoid modification of signaling proteins. Several recent review abstracts are reproduced in an Appendix attached hereto.[5] This has been the trend and focus of those skilled in the art. Researchers studying the anti-cancer effects of statins, for example, currently believe that these effects reside in the property of statins to reduce protein prenylation and not do to the ability of these drugs to reduce cholesterol presence (or absorbtion), *per se*. Thus, the logical extension of this reasoning is to simply state that attacking cholesterol to treat cancer is so unapparent that even though the drugs being tested are known cholesterol inhibitors, other mechanisms, unrelated to cholesterol presence or absorbtion *per se*, are used to explain the anti-cancer effects of these drugs.[6]

The Applicant accordingly respectfully requests that the Examiner withdraw the rejection under 35 USC §103(a).

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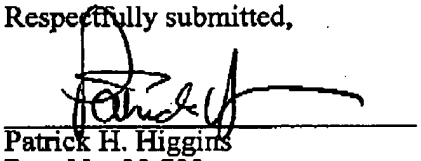
For the foregoing reasons, the Applicant submits that Claims 1-29 are in condition for allowance. Early action toward this end is courteously solicited.

The Commissioner is authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-1943.

Respectfully submitted,



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[5] The Statins As Anticancer Agents, Clin Cancer Res. 2003 Jan;9(1):10-9; Potential Anticancer Effects Of Statins, Endothelium. 2003;10(1):49-58; Potential Antitumor Effects Of Statins (Review), Int J Oncol. 2003 Oct;23(4):1055-69; Studies Of The Isoprenoid-Mediated Inhibition Of Mevalonate Synthesis Applied To Cancer Chemotherapy And Chemoprevention, Exp Biol Med (Maywood). 2004 Jul;229(7):567-85.

[6] Azetidinone compounds are not contemplated suggested or described anywhere in the art be used as a therapeutic agent to control cholesterol-associated tumors.